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Individualized beta-band oscillatory transcranial direct current stimulation over the primary motor cortex enhances corticomuscular coherence and corticospinal excitability in healthy individuals

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ABSTRACT

Background: Simultaneously modulating individual neural oscillation and cortical excitability may be important for enhancing communication between the primary motor cortex and spinal motor neurons, which plays a key role in motor control. However, it is unknown whether individualized beta-band oscillatory transcranial direct current stimulation (otDCS) enhances corticospinal oscillation and excitability.

Objective: This study investigated the effects of individualized beta-band otDCS on corticomuscular coherence (CMC) and corticospinal excitability in healthy individuals.

Methods: In total, 29 healthy volunteers participated in separate experiments. They received the following stimuli for 10 min on different days: 1) 2-mA otDCS with individualized beta-band frequencies, 2) 2-mA transcranial alternating current stimulation (tACS) with individualized beta-band frequencies, and 3) 2-mA transcranial direct current stimulation (tDCS). The changes in CMC between the vertex and tibialis anterior (TA) muscle and TA muscle motor-evoked potentials (MEPs) were assessed before and after (immediately, 10 min, and 20 min after) stimulation on different days. Additionally, 20-Hz otDCS for 10 min was applied to investigate the effects of a fixed beta-band frequency on CMC.

Results: otDCS significantly increased CMC and MEPs immediately after stimulation, whereas tACS and tDCS had no effects. There was a significant negative correlation between normalized CMC changes in response to 20-Hz otDCS and the numerical difference between the 20-Hz and individualized CMC peak frequency before the stimulation.

Conclusions: These findings suggest that simultaneous modulation of neural oscillation and cortical excitability is critical for enhancing corticospinal communication. Individualized otDCS holds potential as a useful method in the field of neurorehabilitation.

Abbreviations: otDCS, oscillatory transcranial direct current stimulation; CMC, corticomuscular coherence; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TA, tibialis anterior; MEP, motor-evoked potential; M1, primary motor cortex; EEG, electroencephalography; EMG, electromyography; TMS, transcranial magnetic stimulation; tES, transcranial electrical stimulation; STDP, spike timing-dependent plasticity.

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1. Introduction

Functional beta-band oscillatory coupling between the primary motor cortex (M1) and spinal motor neurons of active muscles plays a key role in motor control [1–6]. Synchronous oscillatory brain activities can be measured using the coherence of electroencephalographic (EEG) and electromyographic (EMG) signals [7], which represents an established measure of the integrity of the pyramidal system [defined as corticomuscular coherence (CMC)] [5,8,9]. Changes in CMC have been observed after the acquisition of new motor skills in healthy individuals [1,6]. Another study demonstrated that the enhancement of CMC is associated with functional motor recovery in patients after stroke [10–13]. Therefore, new strategies to enhance corticospinal oscillatory coupling are required to improve motor learning and motor function recovery after stroke.

Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) can alter cortical excitability and oscillation in the human cerebral cortex [14]. tDCS polarizes or depolarizes neuronal membrane potential and increases or decreases cortical excitability in a polarity-specific manner [15,16]. tACS can entrain oscillations through the injection of sinusoidal currents by shifting their phase or modulating their power at the stimulation frequency [17–20]. Oscillatory tDCS (otDCS), which includes elements of DC and AC, simultaneously modulates the potential and oscillation activity of neuronal membranes [14,19]. These combined effects effectively determine the endogenous cortical rhythms of the brain [21,22]. Thus, otDCS may represent a useful modality for enhancing corticospinal oscillatory coupling. However, to the best of our knowledge, no previous study investigated the effects of otDCS on corticospinal oscillatory coupling, and the mechanisms underlying these effects remain unclear.

To enhance corticospinal oscillatory coupling, otDCS generally aims to match the intrinsic frequencies of oscillatory neural activity in the target brain [19,23]. Several studies reported that tACS with individualized frequencies enhanced the endogenous power of brain oscillations during stimulation [24,25]. Additionally, membrane voltage exhibited strong periodic fluctuations when the driving frequency was close to the intrinsic frequency [14,26]. Thus, we hypothesized that otDCS with beta-band CMC at the peak frequency of each participant can increase corticospinal oscillatory coupling and cortical excitability after stimulation. To clarify this hypothesis, we investigated the effects of three brain stimulation techniques (otDCS, tACS, and tDCS) on CMC and motor-evoked potential (MEP) using transcranial magnetic stimulation (TMS). We expected that otDCS would enhance corticospinal oscillatory coupling and that both otDCS and tDCS would increase corticospinal excitability [15,27,28]. In contrast, we did not expect tACS to change corticospinal oscillatory coupling and cortical excitability after the stimulation [29]. In addition, we investigated the importance of an individualized beta-band frequency as an otDCS parameter by comparing the responses to the individualized frequency with those resulting from the use of a fixed beta-band frequency.

2. Material and methods

2.1. Participants

A total of 29 healthy volunteers (aged 25 ± 4 years; 12 women) participated in Experiments 1, 2, and 3, each consisting of 19 (aged 25 ± 3 years; 8 women), 19 (aged 25 ± 3 years; 8 women), and 21 (25 ± 4 years; 9 women) healthy volunteers, respectively. The sample size was based on a previous study that investigated the effects of tACS on CMC [30]. None of the participants had a history of neurological and/or orthopedic diseases, and they were not undergoing treatment with any medication that affected the central nervous system. The participants were screened to identify distinctive beta-band CMC during ankle isometric contraction before starting the experiment because a previous study reported that significant CMC was detected in 46% of participants [31]. All the participants provided written informed consent prior to participation in the present study. The study protocol was approved by the local ethics committee of the Yamagata Prefectural University of Health Sciences (approval number: 1860–06), and the study was performed in accordance with the ethical standards of the Declaration of Helsinki.

2.2. General experimental procedure

Three experiments were conducted to investigate the effects of individualized otDCS frequencies on CMC and corticospinal excitability. In the first experiment, we examined the effects of otDCS with individualized beta-band frequencies on CMC. In the second experiment, we explored whether otDCS with individualized beta-band frequencies modulated corticospinal excitability. We employed a crossover design for Experiments 1 and 2, which were conducted on different days to minimize the effects of isometric contraction during CMC assessment on corticospinal excitability [32]. In the third experiment, otDCS at 20 Hz was applied to investigate whether a fixed beta-band frequency increases CMC. The methods for each experiment are described in detail in the following sections.

2.3. Transcranial electrical stimulation (tES)

tES was delivered by a DC Stimulation-Plus (NeuroConn, Ilmenau, Germany) connected to a pair of rubber electrodes. A ring electrode for the anode (inner radius = 1.00 cm, outer radius = 3.75 cm, area = 41.0 cm^2) was placed over the right leg area of the motor cortex. Another oblong electrode for the cathode (area = 35 cm^2) was placed over the right forehead. A ring electrode was used to record EEG signals for the assessment of CMC. The center of the ring electrode was positioned at a vertex (Cz) that was carefully identified using a tape measure according to the international 10–20 system for EEG electrode placement. We previously found that this specific placement of the ring electrode could induce an electric field over the left primary motor cortex [6]. The stimulation frequency for otDCS and tACS was individually targeted at the EEG–EMG peak beta-band frequency before stimulation because an increase in the frequency band has been associated with motor learning and motor recovery following stroke [1,6,10–13]. The stimulus intensity was set at 2 mA for otDCS (sinusoidal waveform with an amplitude between 0 and 2 mA), tACS (sinusoidal waveform with an amplitude between −1 and 1 mA), and tDCS. The stimulation duration was set to 10 min.

2.4. Electrophysiological recordings

EEG and EMG signals were recorded using Ag/AgCl electrodes (10 mm diameter, 20 mm inter-electrode distance). The impedance of electrodes was maintained under 5 kΩ throughout the experiment. The EEG electrodes were placed at the vertex and 5 cm anterior to the vertex because studies have established that CMC is focalized around the vertex for the ankle muscles [1,2,4]. The EMG electrodes were placed at the tibialis anterior (TA) muscle of the right leg. EEG and EMG signals were band-pass–filtered (EEG, 0.05–200 Hz; 5–500 Hz) using Neuropack MEB2200 (NIHON KOHDEN, Tokyo, Japan). Both EEG and EMG signals were sampled at

5000 Hz using NI USB-6363 and LabVIEW 2018 (National Instruments, Austin, TX, USA) and stored on a computer for analysis.

3. CMC

Each participant was comfortably seated in a rigid chair with his/her right foot firmly fastened to a force plate containing a strain gauge that measured the force exerted on the plate. EEG and EMG signals were recorded while the participants performed a static isometric contraction of the TA muscle, in which they were asked to maintain a force level of 10% maximal voluntary contraction for 2 min. The target force level was displayed on the screen as a horizontal line, and the participants were instructed to follow this line as precisely as possible with the moving red trace depicting real-time force production [4]. The frequency-domain correlation between EEG and EMG signals was estimated using the coherence function $|R_{xy}(\lambda)|$. The approximation produced has been thoroughly described previously [7]. In brief, auto-spectra and cross-spectra were computed by isolating signals into non-overlapping data segments. Subsequently, Fourier transformations were performed on these segments, and the data were averaged. The coherence spectrum was then computed from the squared cross-spectrum normalized to the product of the two auto-spectra as follows:

$$|R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda) f_{yy}(\lambda)}$$

Serving as a frequency parallel to the correlation coefficient, coherence reflects an index of the linear association between electrophysiological signals from the cortex and muscle and is quantified as a value between 0 and 1. Each recording was 120 s in duration, and the sampling frequency was 5000 Hz. The segment length was 4096, yielding segments per recording with a spectral resolution of 1.22 Hz. The statistical significance of individual coherence estimates was assessed according to the upper 95% confidence limit, which was given by $1 - (0.05)^{1/(L-1)}$, where L is the number of disjoint sections [7]. Data analyses were conducted using MATLAB® (Math Works, Natick, MA, USA). We adopted otDCS and tACS by setting the stimulation frequency at the EEG–EMG peak beta-band frequency. Corticomuscular coupling in the 15–35-Hz frequency range is greater during periods of steady contraction, and it may reflect the discharge of corticospinal cells [1]. Thus, the peak amplitude of CMC, defined as the difference between the maximum positive amplitude and zero of a waveform, within this frequency range was used for the analysis.

4. TMS

To assess corticospinal excitability, single-pulse TMS was delivered to the M1 responsible for motor representation of the leg with a double-cone coil that was connected to the Magstim 200 (Magstim Co., Whitland, UK). The stimulating coil was located 0–2 cm posterior to the vertex to induce current flow in a posterior to anterior direction in the brain. The optimal coil positioning on the hot spot of the M1 was identified for inducing the largest MEP amplitude in the right TA muscle. The stimulation intensity was adjusted to 120% of the active motor threshold, which was defined as the minimum stimulus intensity that produced 200-μV MEPs with a 50% probability during isometric contraction upon 100-μV EMG of the TA muscle. Fifteen MEPs were recorded while the participants performed an isometric contraction with 100 μV of stimulation [33].

4.1. Experiment 1: Effects of otDCS with individualized beta-band frequencies on CMC

Nineteen healthy volunteers (aged 25 ± 3 years; eight women) participated in a crossover study. The participants randomly received otDCS, tACS, or tDCS on three different days. The order of the stimuli was counterbalanced across the participants. EEG, EMG, and torque signals were recorded to calculate CMC during 2 min of isometric ankle dorsiflexion. First, the baseline CMC data were measured to normalize the data. Next, the main assessments were performed before (Pre), immediately after (Post0), and 10 min (Post10) and 20 min (Post20) after stimulation. To prevent carry-over effects from the previous intervention, washout intervals of at least 3 days were applied between sessions.

4.2. Experiment 2: Effects of otDCS with individualized frequencies on corticospinal excitability

Nineteen healthy volunteers (aged 25 ± 3 years; eight women), 12 of whom participated in Experiment 1, were enrolled in a crossover study. The participants randomly received otDCS, tACS, or tDCS on three different days. To assess changes in motor cortex excitability, we applied single-pulse TMS to the leg motor cortex before and after tES using the same parameters as those in Experiment 1. Before the main assessment, the baseline MEPs were measured to normalize the data. Following a 2-min rest period, MEPs were assessed before (Pre), immediately after (Post0), and 10 min (Post10) and 20 min (Post20) after stimulation.

4.3. Experiment 3: Effects of the fixed beta-band frequency of otDCS on CMC

Twenty-one healthy volunteers (aged 25 ± 4 years; nine women), seven of whom participated in Experiment 1 only and 11 of whom participated in Experiments 1 and 2, were enrolled in a before–after trial. To investigate whether the specific frequency of otDCS increases beta-band CMC, we applied otDCS of 20-Hz to the right leg area of the motor cortex for 10 min using settings identical to those used in Experiment 1. The baseline CMC data were measured to normalize the data. Next, we measured the CMC values before (Pre), immediately after (Post0), 10 min after (Post10), and 20 min after (Post20) stimulation.

4.4. Statistical analysis

The Shapiro–Wilk test was performed to assess the normality of all data. Because all data followed normal distribution ($P \geq 0.05$), we performed the following analysis. Two-way repeated-measures analysis of variance (ANOVA) was performed to assess the effect of the interaction between the stimulus (otDCS, tACS, and tDCS) and time (Pre, Post0, Post10, and Post20) on CMC in Experiment 1 and on MEPs in Experiment 2. Paired *t*-tests with Bonferroni's correction were employed for post-hoc analyses. For Experiment 3, one-way repeated-measured ANOVA was performed to assess the main effect of time (Pre, Post0, Post10, and Post20) on CMC. We hypothesized that 20-Hz otDCS increases CMC when the individual CMC peak frequency is closer to 20 Hz. To test this hypothesis, Pearson's correlation analysis was performed to investigate the relationship between changes in normalized CMC and individual CMC peak frequencies in Experiment 3. Changes in normalized CMC were calculated by subtracting the normalized CMC data at Pre from that at Post0. Individual CMC peak frequencies were calculated as the numerical difference between the 20-Hz and individual CMC peak values before the stimulation. All statistical comparisons were

performed using SPSS Statistics 24 (IBM, Armonk, NY, USA). Statistical significance was set at $P < 0.05$ for all comparisons.

5. Results

5.1. Experiment 1

The mean CMC (standard deviation) values in response to otDCS, tACS, and tDCS at baseline were 0.09 (0.14), 0.11 (0.13), and 0.09 (0.12), respectively. No significant main effect of the stimulation task was observed at baseline [$F_{(2, 36)} = 2.01$, $P = 0.15$].

otDCS immediately enhanced beta-band CMC, whereas tACS and tDCS yielded no changes (Fig. 1). These results were supported by a statistically significant interaction between time and stimulation task [$F_{(6, 108)} = 2.36$, $P = 0.035$]. The main effect of time was also significant [$F_{(3, 54)} = 6.21$, $P = 0.001$]. The stimulation task as a main effect was not statistically significant [$F_{(2, 36)} = 1.06$, $P = 0.36$]. Post-hoc analyses revealed that otDCS resulted in a significant increase in CMC at Post0 compared with that at Pre ($P = 0.0004$). A comparison of CMC values among stimulation tasks at Post0 revealed significantly higher values in response to otDCS than that in response to tACS ($P = 0.009$). To confirm the robust effect of otDCS on CMC at Post0, we compared the CMC of tACS and tDCS at Pre using one-tailed Student's t-test based on the hypothesis that CMC and MEPs increase after otDCS according to the above-mentioned results. The analysis revealed significantly higher CMC in response to the otDCS condition at Post0 than that in response to the tACS and tDCS conditions at Pre (both $P < 0.05$). The raw data for CMC amplitudes are provided in the Supplementary Materials.

5.2. Experiment 2

The mean raw amounts (standard deviation) of the MEPs at baseline were 0.62 (0.20) mV for otDCS, 0.72 (0.28) mV for tACS, and 0.66 (0.37) mV for tDCS. No significant main effect of the stimulation task was observed at baseline [$F_{(2, 36)} = 0.87$, $P = 0.43$].

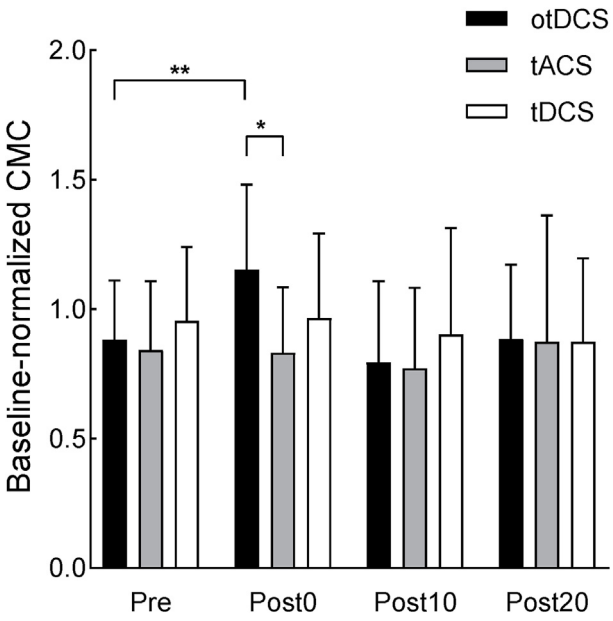

Fig. 1. The effect of oscillatory transcranial direct current stimulation (otDCS), transcranial alternating current stimulation (tACS), and transcranial direct current stimulation (tDCS) on normalized corticomuscular coherence (CMC). The CMC values are normalized to the baseline values. The values are presented as the mean ± standard deviation. Black (otDCS), gray (tACS), and white bars (tDCS) indicate the time course of the CMC before (Pre), immediately after (Post0), and 10 (Post10) and 20 min (Post20) after stimulation. Asterisks indicate significant differences between the time course and within the interventions (*$P < 0.01$, **$P < 0.001$).

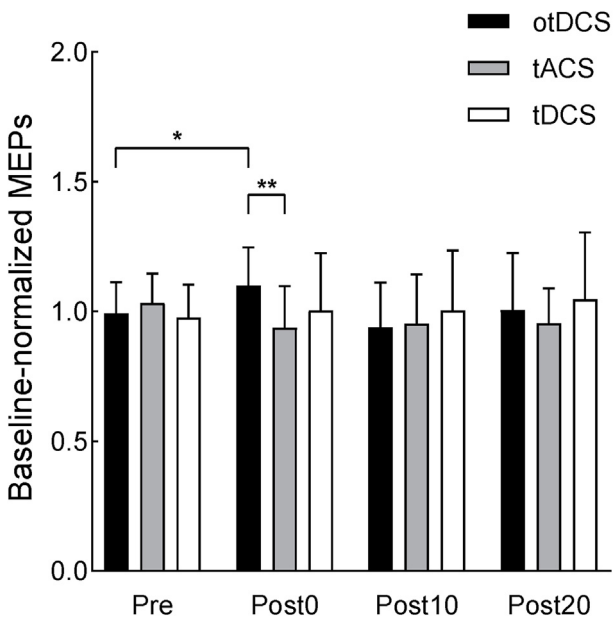

Fig. 2. The effect of oscillatory transcranial direct current stimulation (otDCS), transcranial alternating current stimulation (tACS), and transcranial direct current stimulation (tDCS) on normalized motor evoked potentials (MEPs). The MEPs are normalized to the baseline values. The values are presented as the mean ± standard deviation. Black (otDCS), gray (tACS), and white bars (tDCS) indicate the time course of MEPs before (Pre), immediately after (Post0), and 10 (Post10) and 20 min (Post20) after stimulation. Asterisks indicate significant differences between the time course and within the interventions (*$P < 0.05$, **$P < 0.01$).

otDCS led to an immediate increase in corticospinal excitability, but no changes were observed after tACS and tDCS (Fig. 2). These results were confirmed by two-way repeated-measures ANOVA, which revealed significant interactions between time and stimulation task [$F_{(6, 108)} = 2.76$, $P = 0.016$]. There was no main effect of time [$F_{(3, 54)} = 1.28$, $P = 0.29$] and stimulation task [$F_{(2, 36)} = 0.54$, $P = 0.59$]. Post-hoc analyses revealed that otDCS significantly increased MEPs at Post0 compared with those at Pre ($P = 0.011$). At Post0, the MEPs for otDCS were significantly higher than those for tACS ($P = 0.003$). One-tailed Student's t-test was used to confirm the robust effect of otDCS on MEPs at Post0. This analysis indicated that MEPs in the otDCS condition at Post0 were significantly higher than the MEPs in the tACS and tDCS conditions at Pre (both $P < 0.05$).

5.3. Experiment 3

The time course of normalized CMC is presented in Fig. 3. One-way repeated-measures ANOVA revealed no significant main effect of time [$F_{(3, 60)} = 1.47$, $P = 0.23$], indicating that 20-Hz otDCS did not affect CMC. However, there was a significant negative correlation between the changes in normalized CMC and the numerical difference between the 20-Hz and individual CMC peak frequencies ($r = -0.556$, $P = 0.009$; Fig. 4).

6. Discussion

This study shows that otDCS with individualized beta-band frequencies, but not tACS or tDCS, increased CMC and MEPs immediately after stimulation. Moreover, normalized changes in CMC induced by 20-Hz otDCS were correlated with the numerical

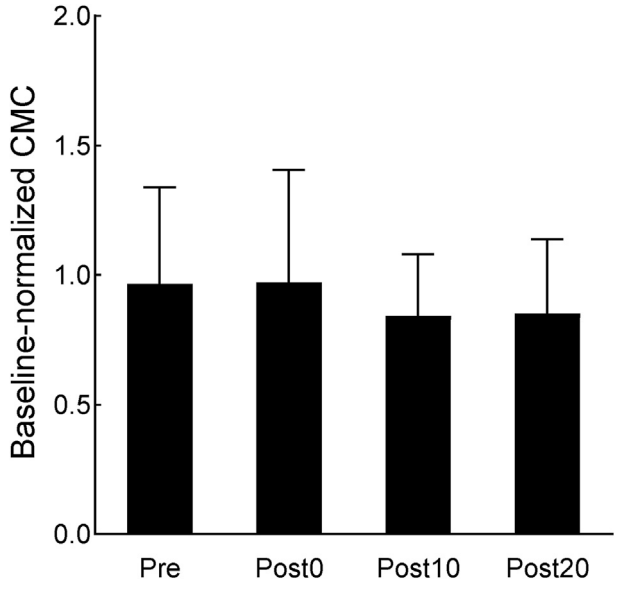

Fig. 3. The effect of 20-Hz oscillatory transcranial direct current stimulation (otDCS) on normalized corticomuscular coherence (CMC). The CMC values are normalized to the baseline values. The values are presented as the mean ± standard deviation. Black bars indicate the time course of CMC before (Pre), immediately after (Post0), and 10 (Post10) and 20 min (Post20) after stimulation.

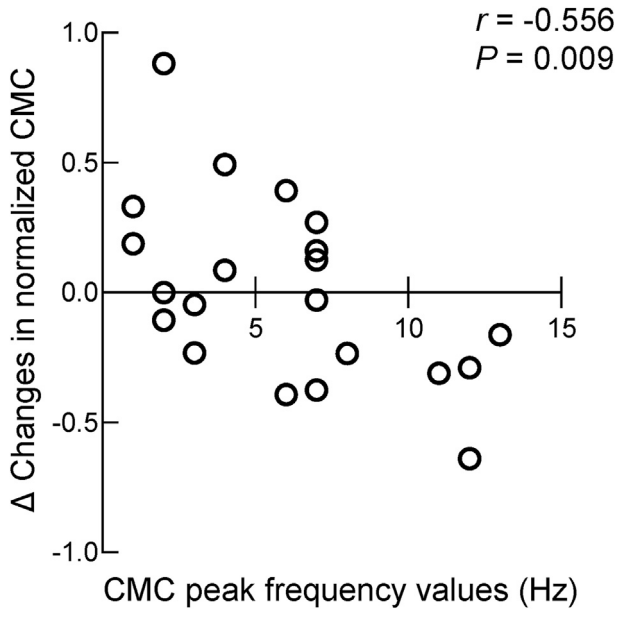

Fig. 4. Correlations between changes in normalized corticomuscular coherence (CMC) following 20-Hz oscillatory transcranial direct current stimulation (otDCS) and the numerical difference between the 20-Hz and individual CMC peak frequency before the stimulation. The delta changes in normalized CMC were calculated by subtracting the baseline values from those immediately after 20-Hz otDCS. The CMC peak frequency values show the numerical difference between the 20-Hz and individual CMC peak frequency before the stimulation.

distance between 20 Hz and the individual CMC peak beta-band frequency before the stimulation, indicating that 20-Hz otDCS increased CMC when the individual CMC peak frequency was closer to 20 Hz. Our findings provide the first evidence that otDCS with individualized oscillatory activity at beta frequency can enhance the communication between the motor cortex and spinal motor neurons.

6.1. Effects of otDCS with individual frequencies on CMC

The enhancement of CMC, which reflects pyramidal system activity, leads to an increase in the functional coupling between M1 and spinal motor neurons [5,8,9]. The reason for this enhancement is that otDCS, which possesses elements of AC and DC, might increase and enhance the entrainment of corticospinal pyramidal neuron oscillation in M1 [14]. tACS at the frequency of endogenous neural oscillation modulates the spike timing of inhibitory and excitatory neurons without changing the average firing rate [14]. Anodal tDCS affects the firing rate by increasing glutamate and GABA levels [14,16]. Furthermore, several studies reported that the effects of tACS are more pronounced online to stimulation when entrainment is more prominent [25,29,34,35]. Therefore, the summations of enhancement spike timing and increases in the firing rate induced by otDCS may have enhanced the targeted CMC in the present study. This hypothesis is supported by the results of Experiment 3, in which participants with CMC peak frequencies closer to 20 Hz displayed increased CMC in response to otDCS of 20-Hz. These results could be attributable to spike timing-dependent plasticity (STDP), which postulates that the repetitive input similar to resonance frequency is strengthened according to the STDP rule during stimulation [24,36]. These data supported our findings that individualization of the beta-band frequency of otDCS could represent a valid strategy for enhancing communication in corticospinal pathways between M1 and spinal motor neurons.

6.2. Effects of otDCS with individualized frequencies on corticospinal excitability

The corticospinal excitability of the TA muscle increased after otDCS but not after tACS and tDCS. In agreement with previous studies on tACS using individualized or fixed beta-band frequencies over M1, no offline effects on corticospinal excitability were observed [29,37,38]. This is supported by another study that reported that tACS genuinely entrains neural network activity during stimulation, whereas the effects did not persist when the stimulus was withdrawn [35]. Thus, the effects of tACS on corticospinal excitability may only reflect the ongoing stimulation.

Our results disagree with those of a previous study, which revealed that anodal tDCS could temporarily increase corticospinal excitability in healthy individuals [15,27,28]. Many studies found that 20%–60% of individuals experienced a classical increase in excitability following a single anodal tDCS session, whereas the remaining participants experienced no change or exhibited a decrease compared with baseline values [39]. Additionally, a recent large study reported that tDCS does not reliably affect cortical excitability [40]. tDCS modulates the resting membrane potential of neuronal populations via ionic adjustment of the extracellular space and synaptic activity in a manner similar to long-term potentiation [41]. However, in the absence of changes in the balance of excitability and inhibitory drive that is assumed to underlie beta oscillatory activity, tDCS fails to change synaptic strength [42]. In fact, TMS delivered at a particular phase of beta oscillation induced MEPs with greater amplitude and less variability based on state-dependent gain modulation [43–46]. Thus, tDCS, which did not alter the specific oscillation, might be more variable.

In contrast, otDCS can change the resting membrane potential for depolarization and the firing pattern of the stimulated neurons [14,19]. In vitro experiments revealed that neuronal network activity can be entrained by sinusoidal electric fields with an intensity similar to that of the endogenous electric field of that network [26]. To increase corticospinal excitability, it may be essential for AC to superimpose onto DC to induce neuronal depolarization [27,28].

6.3. The relationship between changes in CMC and MEPs induced by otDCS with individualized frequencies

It is speculated that increased corticospinal excitability induced by otDCS depends on the enhancement of beta-band CMC. A study reported a correlation between CMC and changes in MEP induced by peripheral electrical stimulation [47]. Another study reported that cortical oscillation modulates the firing rate of motor cortical efferent commands [48]. Therefore, the increase in beta activity induced by otDCS in the motor cortex involving pyramidal neurons may increase corticospinal output as an index of MEP in response to TMS [43–46]. However, in the present study, CMC and MEPs were measured in separate experiments. Further research is needed to simultaneously examine the changes of corticospinal communication and excitability induced by otDCS.

6.4. Clinical applications

Previous studies reported that poor communication between the M1 and spinal motor neurons may reflect an underlying mechanism that causes movement disorders in patients with stroke [49,50]. Increasing beta-band CMC is associated with motor learning in healthy individuals and motor function recovery after stroke [1,6,10–13]. otDCS may be effective as an adjuvant therapy with rehabilitation, whereas its long-term effects may promote motor recovery after stroke.

7. Limitations

The sample size of the present study was relatively small. Hence, some results, such as the lack of differences between the otDCS and tDCS conditions for CMC and MEPs immediately after the stimulation, should be interpreted with caution. Additionally, the study included healthy participants having distinctive beta-band CMC values. A previous study reported that patients with nervous system disorders have lower CMC than healthy participants [5]. Thus, it is unclear whether similar results would be obtained in participants with no significant beta-band CMC. Further research is needed to investigate the effects of otDCS with individualized beta-band frequencies on CMC and motor performance in patients after stroke.

8. Conclusions

The present study indicates that otDCS with individualized beta-band frequencies increased CMC and MEPs in healthy individuals, whereas tACS and tDCS had no such effects, suggesting that modulation of the firing pattern and rate of M1 with individualized frequencies plays an important role in simultaneously enhancing corticospinal oscillation and excitability. However, no significant difference was observed between the otDCS and tDCS conditions after the stimulation. Further studies are warranted to clarify the clinical application of otDCS with individualized beta-band frequencies in patients with neurological disorders.

CRediT authorship contribution statement

Daisuke Kudo: Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Tadaki Koseki:** Investigation, Writing – review & editing. **Natsuki Katagiri:** Investigation, Writing – review & editing. **Kaito Yoshida:** Writing – review & editing. **Keita Takano:** Writing – review & editing. **Masafumi Jin:** Writing – review & editing. **Mitsuhiro Nito:** Writing – review & editing. **Shigeo Tanabe:** Software, Resources, Writing – review & editing. **Tomofumi Yamaguchi:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.11.004.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Perez MA, Lundbye-Jensen J, Nielsen JB. Changes in corticospinal drive to spinal motoneurones following visuo-motor skill learning in humans. Physiol 2006;573:843–55. https://doi.org/10.1113/jphysiol.2006.105361.
[2] Petersen TH, Willerslev-Olsen M, Conway BA, Nielsen JB. The motor cortex drives the muscles during walking in human subjects. J Physiol 2012;590:2443–52. https://doi.org/10.1113/jphysiol.2012.227397.
[3] Mendez-Balbuena I, Huethe F, Schulte-Mönting J, Leonhart R, Manjarrez E, Kristeva R. Corticomuscular coherence reflects interindividual differences in the state of the corticomuscular network during low-level static and dynamic forces. Cerebr Cortex 2012;22:628–38. https://doi.org/10.1093/cercor/bhr147.
[4] Spedden ME, Nielsen JB, Geertsen SS. Oscillatory corticospinal activity during static contraction of ankle muscles is reduced in healthy old versus young adults. Neural Plast 2018;2018:3432649. https://doi.org/10.1155/2018/3432649.
[5] Liu J, Sheng Y, Liu H. Corticomuscular coherence and its applications: a review. Front Hum Neurosci 2019;13:100. https://doi.org/10.3389/fnhum.2019.00100.
[6] Yamaguchi T, Svane C, Forman CR, Beck MM, Geertsen SS, Lundbye-Jensen J, et al. Transcranial alternating current stimulation of the primary motor cortex after skill acquisition improves motor memory retention in humans: a double-blinded sham-controlled study. Cereb Cortex Comm 2020;1:1–11. https://doi.org/10.1093/texcom/tgaa047.
[7] Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF. A framework for the analysis of mixed time series/point process data–theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. Prog Biophys Mol Biol 1995;64:237–78. https://doi.org/10.1016/s0079-6107(96)00009-0.
[8] Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AI, et al. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol 1995;489:917–24. https://doi.org/10.1113/jphysiol.1995.sp021104.
[9] Mima T, Hallett M. Corticomuscular coherence: a review. J Clin Neurophysiol 1999;16:501–11. https://doi.org/10.1097/00004691-199911000-00002.
[10] Belardinelli P, Laer L, Ortiz E, Braun C, Gharabaghi A. Plasticity of premotor cortico-muscular coherence in severely impaired stroke patients with hand paralysis. Neuroimage Clin 2017;14:726–33. https://doi.org/10.1016/j.nicl.2017.03.005.
[11] Zheng Y, Peng Y, Xu G, Li L, Wang J. Using corticomuscular coherence to reflect function recovery of paretic upper limb after stroke: a case study. Front Neurol 2017;8:728. https://doi.org/10.3389/fneur.2017.00728.
[12] Pan LH, Yang WW, Kao CL, Tsai MW, Wei SH, Fregni F, et al. Effects of 8-week sensory electrical stimulation combined with motor training on EEG-EMG coherence and motor function in individuals with stroke. Sci Rep 2018;8:9217. https://doi.org/10.1038/s41598-018-27553-4.
[13] Krauth R, Schwertner J, Vogt S, Lindquist S, Sailer M, Sickert A, et al. Corticomuscular coherence is reduced acutely post-stroke and increases bilaterally during motor recovery: a pilot study. Front Neurol 2019;10:126. https://doi.org/10.3389/fneur.2019.00126.
[14] Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci 2013;7:279. https://doi.org/10.3389/fnhum.2013.00279.

[15] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.
[16] Das S, Holland P, Frens MA, Donchin O. Impact of transcranial direct current stimulation (tDCS) on neuronal functions. Front Neurosci 2016;10:550. https://doi.org/10.3389/fnins.2016.00550.
[17] Reato S, Rahman A, Bikson M, Parra LC. Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. Front Hum Neurosci 2013;7:687. https://doi.org/10.3389/fnhum.2013.00687.
[18] Helfrich RF, Schneider TR, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr Biol 2014;24:333–9. https://doi.org/10.1016/j.cub.2013.12.041.
[19] Veniero D, Vossen A, Gross J, Thut G. Lasting EEG/MEG aftereffects of rhythmic transcranial brain stimulation: level of control over oscillatory network activity. Front Cell Neurosci 2015;9:477. https://doi.org/10.3389/fncel.2015.00477.
[20] Tavakoli AV, Yun K. Transcranial alternating current stimulation (tACS) mechanisms and protocols. Front Cell Neurosci 2017;11:214. https://doi.org/10.3389/fncel.2017.00214.
[21] Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444:610–3. https://doi.org/10.1038/nature05278.
[22] Kirov R, Weiss C, Siebner HR, Born J, Marshall L. Slow oscillation electrical brain stimulation during waking promotes EEG theta activity and memory encoding. Proc Natl Acad Sci USA 2009;106:15460–5. https://doi.org/10.1073/pnas.0904438106.
[23] Vulić K, Bjekić J, Paunović D, Jovanović M, Milanović S, Filipović SR. Theta-modulated oscillatory transcranial direct current stimulation over posterior parietal cortex improves associative memory. Sci Rep 2021;11:3013. https://doi.org/10.1038/s41598-021-82577-7.
[24] Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One 2010;5:e13766. https://doi.org/10.1371/journal.pone.0013766.
[25] Neuling T, Rach S, Herrmann CS. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front Hum Neurosci 2013;7:161. https://doi.org/10.3389/fnhum.2013.00161.
[26] Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron 2010;67:129–43. https://doi.org/10.1016/j.neuron.2010.06.005.
[27] Bergmann TO, Groppa S, Seeger M, Mölle M, Marshall L, Siebner HR. Acute changes in motor cortical excitability during slow oscillatory and constant anodal transcranial direct current stimulation. J Neurophysiol 2009;102:2303–11. https://doi.org/10.1152/jn.00437.2009.
[28] Groppa S, Bergmann TO, Siems C, Mölle M, Marshall L, Siebner HR. Slow-oscillatory transcranial direct current stimulation can induce bidirectional shifts in motor cortical excitability in awake humans. Neuroscience 2010;166:1219–25. https://doi.org/10.1016/j.neuroscience.2010.01.019.
[29] Schilberg L, Engelen T, Ten Oever S, Schuhmann T, de Gelder B, de Graaf TA, et al. Phase of beta-frequency tACS over primary motor cortex modulates corticospinal excitability. Cortex 2018;103:142–52. https://doi.org/10.1016/j.cortex.2018.03.001.
[30] Wach C, Krause V, Moliadze V, Paulus W, Schnitzler A, Pollok B. The effect of 10 Hz transcranial alternating current stimulation (tACS) on corticomuscular coherence. Front Hum Neurosci 2013;7:511. https://doi.org/10.3389/fnhum.2013.00511.
[31] Ushiyama J, Suzuki T, Masakado Y, Hase K, Kimura A, Liu M, et al. Between-subject variance in the magnitude of corticomuscular coherence during tonic isometric contraction of the tibialis anterior muscle in healthy young adults. J Neurophysiol 2011;106:1379–88. https://doi.org/10.1152/jn.00193.2011.
[32] Thirugnanasambandam N, Sparing R, Dafotakis M, Meister IG, Paulus W, Nitche MA, et al. Isometric contraction interferes with transcranial direct current stimulation (tDCS) induced plasticity: evidence of state-dependent neuromodulation in human motor cortex. Restor Neurol Neurosci 2011;29:311–20. https://doi.org/10.3233/RNN-2011-0601.
[33] Cacchio A, Cimini N, Alosi P, Santilli V, Marrelli A. Reliability of transcranial magnetic stimulation-related measurements of tibialis anterior muscle in healthy subjects. Clin Neurophysiol 2009;120:414–9. https://doi.org/10.1016/j.clinph.2008.11.019.
[34] Pogosyan A, Gaynor LD, Eusebio A, Brown P. Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol 2009;19:1637–41. https://doi.org/10.1016/j.cub.2009.07.074.
[35] Pozdniakov I, Vorobiova AN, Galli G, Rossi S, Feurra M. Online and offline effects of transcranial alternating current stimulation of the primary motor cortex. Sci Rep 2021;11:3854. https://doi.org/10.1038/s41598-021-83449-w.
[36] Markram H, Lübke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 1997;275:213–5. https://doi.org/10.1126/science.275.5297.213.
[37] Antal A, Boros K, Poreisz C, Chaieb L, Terney D, Paulus W. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul 2008;1:97–105. https://doi.org/10.1016/j.brs.2007.10.001.
[38] Nakazono H, Ogata K, Kuroda T, Tobimatsu S. Phase and frequency-dependent effects of transcranial alternating current stimulation on motor cortical excitability. PLoS One 2016;11:e0162521. https://doi.org/10.1371/journal.pone.0162521.
[39] Bashir A, Ahmad S, Alatefi M, Hamza A, Sharaf M, Fecteau S, Yoo WK. Effects of anodal transcranial direct current stimulation on motor evoked potentials variability in humans. Phys Rep 2019;7:e14087. https://doi.org/10.14814/phy2.14087.
[40] Jonker ZD, Gaiser C, Tulen JHM, Ribbers GM, Frens MA, Selles RW. No effect of anodal tDCS on motor cortical excitability and no evidence for responders in a large double-blind placebo-controlled trial. Brain Stimul 2021;14:100–9. https://doi.org/10.1016/j.brs.2020.11.005.
[41] Horvath JC, Carter O, Forte JD. Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). Front Syst Neurosci 2014;8:2. https://doi.org/10.3389/fnsys.2014.00002.
[42] Hanley CJ, Singh KD, McGonigle DJ. Transcranial modulation of brain oscillatory responses: a concurrent tDCS-MEG investigation. Neuroimage 2016;140:20–32. https://doi.org/10.1016/j.neuroimage.2015.12.021.
[43] Torrecillos F, Falato E, Pogosyan A, West T, Di Lazzaro V, Brown P. Motor cortex inputs at the optimum phase of beta cortical oscillations undergo more rapid and less variable corticospinal propagation. J Neurosci 2020;40:369–81. https://doi.org/10.1523/JNEUROSCI.1953-19.2019.
[44] Khademi F, Royter V, Gharabaghi A. Distinct beta-band oscillatory circuits underlie corticospinal gain modulation. Cerebr Cortex 2018;28:1502–15. https://doi.org/10.1093/cercor/bhy016.
[45] Khademi K, Royter V, Gharabaghi A. State-dependent brain stimulation: power or phase? Brain Stimul 2019;12:296–9. https://doi.org/10.1016/j.brs.2018.10.015.
[46] Naros G, Lehnertz T, Leão MT, Ziemann U, Gharabaghi A. Brain state-dependent gain modulation of corticospinal output in the active motor system. Cerebr Cortex 2020;30:371–81. https://doi.org/10.1093/cercor/bhz093.
[47] Koseki T, Kudo D, Katagiri N, Namba S, Nito M, Tanabe S, et al. Electrical stimulation of the common peroneal nerve and its effects on relationship between corticomuscular coherence and motor control in healthy adults. BMC Neurosci 2021;22:61. https://doi.org/10.1186/s12868-021-00665-w.
[48] Salenius S, Portin K, Kajola M, Salmelin R, Hari R. Cortical control of human motoneuron firing during isometric contraction. J Neurophysiol 1997;77:3401–5. https://doi.org/10.1152/jn.1997.77.6.3401.
[49] Mima T, Toma K, Koshy B, Hallett M. Coherence between cortical and muscular activities after subcortical stroke. Stroke 2001;32:2597–601. https://doi.org/10.1161/hs1101.098764.
[50] Fang Y, Daly JJ, Sun J, Hvorat K, Fredrickson E, Pundik S, et al. Functional corticomuscular connection during reaching is weakened following stroke. Clin Neurophysiol 2009;120:994–1002. https://doi.org/10.1016/j.clinph.2009.02.173.